Thromboembolic events after aortic valve replacement in elderly patients with a Carpentier-Edwards Perimount pericardial bioprosthesis

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Objectives: Thromboembolic events after aortic valve replacement with a bioprosthesis were the most frequently occurring complications in elderly patients. Whether this was valve related or dependent on other factors needed further exploration.

Methods: Five hundred patients with a median age of 73 years were followed retrospectively after aortic valve replacement with a pericardial prosthesis for occurrence of thromboembolism. Of these, 348 also underwent coronary artery bypass grafting. Twenty-five factors were investigated for their potential effect by using univariate and multivariate analysis.

Results: Univariate analysis revealed 6 significant factors: preoperative endocarditis ($P = .0001$), preoperative cerebrovascular accident ($P = .002$), use of postoperative warfarin sodium (Coumadin, DuPont Merck; $P = .006$), arterial hypertension ($P = .023$), size of valve prosthesis of 27 mm or larger ($P = .023$), and hospital thromboembolism ($P = .040$). There was a trend toward increased fatal thromboembolism in patients without medication. With a multivariate analysis, 4 factors remained significant: preoperative cerebrovascular accident (risk ratio, 4.8; $P = .0016$), warfarin sodium (risk ratio, 3.0; $P = .0028$), preoperative endocarditis (risk ratio, 5.6; $P = .006$), and hospital thromboembolism (risk ratio, 6.1; $P = .016$). Hypertension had a borderline effect. Age, sex, diabetes, 4 coronary artery factors, 3 other valvular factors, atrial fibrillation, and carotid artery disease had no significant effect.

Conclusions: Some emboli seemed triggered by the valve prosthesis. A proper anticoagulant protocol but also a treatment of hypertension is important in the prevention of thromboembolism after aortic valve replacement with a bioprosthesis. We did not find a significant role of atrial fibrillation and carotid artery disease.

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Received for publication June 19, 2003; revisions requested Oct 29, 2003; accepted for publication Nov 4, 2003.

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J Thorac Cardiovasc Surg 2004;127:1166-70

0022-5223/$30.00

doi:10.1016/j.jtcvs.2003.11.010

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Thromboembolic events after an aortic valve replacement with a bioprosthesis are a considerable part of the postoperative morbidity in elderly patients. Our objectives are identification of the risk factors for thromboembolism and recommendation of therapeutic measures in their prevention. Guidelines for reporting morbidity and mortality after cardiac valvular operations defined neurologic nonhemorrhagic deficits and peripheral arterial emboli as thromboembolic events until otherwise proved.[1] This definition, however, seemed too large and could include thromboembolic events caused by other factors, such as hypertension, atrial fibrillation, other cardiac factors, and carotid artery disease. Thromboembolic events after aortic valve replacement with a bioprosthesis have been linked to the vascular

TABLE 1. Univariate relationship between significant risk factors and occurrence of thromboembolism: the 5-year event-free rate for the factor present and absent and the *P* value as obtained from univariate analysis (Kaplan-Meier method)

Factor	TE/n	Fatal	CVA	RIND	TIA	5-y event-free ± SE		*P* value
						Factor present	Factor absent	
pCVA	5/26	2	2	0	0	0.79 ± 0.09	0.92 ± 0.02	.002
WARF	11/74	2	8	0	1	0.81 ± 0.06	0.93 ± 0.02	.006
AHT (>140/90)	32/349	12	13	1	6	0.90 ± 0.02	0.97 ± 0.02	.023
27+	11/85	2	4	0	5	0.81 ± 0.06	0.94 ± 0.01	.023
hTE	2/9	0	2	0	0	0.60 ± 0.22	0.92 ± 0.02	.040

TE, Number of patients with thromboembolism; *n,* number of patients with factor present; *CVA,* cerebrovascular accident; *RIND,* reversible ischemic neurologic deficit; *TIA,* transient ischemic attack; *pCVA,* preoperative cerebrovascular accident; *WARF,* postoperative use of warfarin sodium; *AHT,* arterial hypertension; *27+,* prosthesis size of 27 mm or larger; *hTE,* hospital thromboembolism.

status in earlier reports.[2,3] This is of particular importance in elderly patients, in whom cardiac and vascular comorbidity is more common. In these patients carotid artery disease can be screened preoperatively by using a Doppler ultrasonographic technique. The role of anticoagulant medication in the occurrence of postoperative thromboembolic events in patients with chronic atrial fibrillation, preoperative cerebrovascular accidents (CVAs), and postoperative cardiac events also required exploration.

Patients and Methods

Five hundred consecutive patients receiving a Carpentier-Edwards Perimount pericardial valve in the aortic position were investigated retrospectively from 1986 through 2001. In 152 patients only the aortic valve was replaced; the other 348 patients had a concomitant procedure, such as a coronary artery bypass grafting (CABG), a procedure on the ascending aorta (n = 27), or a mitral annuloplasty (n = 13). Patients receiving valves in other positions or mechanical valves were excluded. All patients were operated on through a median sternotomy with standard cardiopulmonary bypass, hemodilution, and moderate general body hypothermia. Myocardial protection was obtained with orthograde and retrograde administration of a crystalloid cardioplegia solution and topical cooling with sludge ice.

Potential risk factors that could influence postoperative thromboembolic events were recorded. Previous endocarditis was considered a separate entity.

Warfarin sodium (Coumadin, DuPont Merck) was started on the day the thoracic drains were removed and continued for 3 months. It was continued only in the presence of other indications, mostly atrial fibrillation. Antiplatelet (160 mg aspirin daily) drugs were started in most other patients.

Follow-up was performed by using a questionnaire sent to cardiologists. Specific attention was given to neurologic deficits and peripheral arterial emboli. In all patients with a neurologic deficit, a computed axial tomography (CAT) scan was performed to exclude hemorrhage. The thromboembolic events were graded as transient ischemic attack (TIA; resolving within 30 minutes), reversible ischemic neurologic deficit (RIND; resolving within 24 hours), CVA (ie, with lasting sequelae), or fatal event.

Statistical analysis was performed in a univariate approach by using the Kaplan-Meier method to determine which of the potential factors could be of significant prognostic importance. In the multivariate approach the Cox proportional hazards model was used to directly relate patient characteristics to the risk of a thromboembolic event. A χ^2 analysis was performed to investigate the interrelation of categoric variables. Hospital thromboembolism is defined as the occurrence of the event in the first 30 days after the operation or in the same hospital period if this exceeded 30 days. Long-term thromboembolism is defined as the occurrence of this event after 30 days postoperatively or after discharge if the hospital stay exceeded 30 days.

Results

Preoperative Data and Postoperative Thromboembolism

There were 500 patients (271 male and 229 female patients) with a median age of 73 years (interquartile range, 71-77 years). They had a median ejection fraction of 65%, (interquartile range, 51%-77%). The mean follow-up was 4.2 years, with a total of 2022 patient-years. Nineteen patients died within the first 30 days, and a total of 139, or 6.9% per patient-year, died during follow-up. During hospital stay, a thromboembolic event, confirmed by means of CAT scanning, occurred in 12 patients. In 3 patients this event was fatal. The event was a CVA in 5 patients, a RIND in 1 patient, and a TIA in 3 patients. None of the investigated factors had a significant effect on hospital thromboembolism. Of the 9 surviving patients, 2 had a long-term thromboembolism, and none received warfarin sodium.

During long-term follow-up, a thromboembolic event, also confirmed by means of CAT scanning, occurred in 36 patients, (ie, 1.8% per patient-year). In 12 patients these were fatal; in 15 patients these events were CVAs (in one as a result of a postoperative endocarditis, which was treated medically). The event was a RIND in 2 patients and a TIA in 6 patients. One patient had an event in the lower limbs.

Individual Relationship of Patient Characteristics to Risk of Thromboembolism

Table 1 shows the univariate analysis for the investigated factors, of which 5 had a significant effect on long-term

TABLE 2. Univariate relationship between potential but nonsignificant risk factors and occurrence of thromboembolism: *P* value obtained from univariate analysis (Kaplan-Meier method)

Factor	n	Patients with TE	*P* value
Valvular			
Gradient across aortic valve >75 mm Hg	246	21	.19
Aortic valve regurgitation of grade II or more	156	10	.50
Previously performed aortic valve replacement	15	2	.35
Cardiac			
Crossclamping time >75 min	115	9	.28
Previously performed CABG	35	3	.29
Implantation of ≥4 bypasses	59	6	.29
Coronary artery disease on angiography	327	26	.43
Preoperative atrial fibrillation	83	7	.56
Preoperative Q-wave myocardial infarction	61	5	.67
Postoperative chronic atrial fibrillation	105	10	.68
Episode of atrial fibrillation within the hospital	189	12	.81
Mitral annuloplasty	13	1	.98
Vascular			
Tailoring of the ascending aorta	27	2	.87
Carotid artery disease on duplex scan	53	3	.88
Postoperative use of antiplatelet drugs	220	12	.10
General			
Male sex	271	23	.18
Age over the median (73 y)	250	23	.19
Carcinoma in preoperative history	53	4	.50
Diabetes mellitus	47	4	.82

TE, Thromboembolism; *n,* number of patients with factor present; *CABG,* coronary artery bypass grafting.

thromboembolism. Preoperative endocarditis is considered a separate entity: 3 of the 8 patients had a thromboembolic event that was fatal, but none of the patients had signs of sepsis. The 5-year event-free rate for thromboembolism in patients with previous endocarditis was 0.28 ± 0.23 versus 0.92 ± 0.02 in patients without this condition ($P = .0001$).

Preoperative CVA was significantly more common in patients with a positive duplex scan result (11.3% vs 4.5%, $P < .049$). The severity of aortic valve stenosis was not different between patients with a positive duplex scan result and those with a negative duplex scan result: the median gradients across the valve were 75 mm Hg (60-100 mm Hg) versus 74 mm Hg (55-94 mm Hg), respectively. Seven patients with a positive duplex scan result underwent simultaneous carotid endarterectomy. They did not have any postoperative thromboembolic events.

The main reason for treatment with warfarin sodium was preoperative atrial fibrillation (41.0% vs 9.6%, $P < .001$). Another reason was preoperative myocardial infarction (26.2% vs 13.2%, $P = .007$). There was a trend toward postoperative use of warfarin sodium in patients with decreased left ventricular function (19.2% vs 13.4%, $P = .096$), preoperative CVA (23.3% vs 14.0%, $P = .10$), and prior aortic valve replacement (33.3% vs 14.2%, $P = .109$). Patients older than 80 years took significantly less warfarin sodium (5.0% vs 16.1%, $P = .036$). In 105 patients with postoperative chronic atrial fibrillation, 4 of 44 patients receiving warfarin sodium, 1 of 35 patients receiving acetylsalicylic acid, and 3 of 26 patients receiving no medication had an event. In 374 patients without atrial fibrillation, 7 of 30 patients receiving warfarin sodium, 12 of 185 patients receiving acetylsalicylic acid, and 10 of 159 patients receiving no medication had an event. There was a trend toward an increase in fatal events in patients taking no medication compared with in those taking acetylsalicylic acid (8/206 vs 2/220, $P = .091$).

Table 2 shows the nonsignificant parameters. Age greater than the median did not result in a significant increase in thromboembolism. Using age as a continuous variable, we found no significant difference ($P = .14$).

Simultaneous Relationship of Patient Characteristics to the Risk of Thromboembolism

Table 3 shows the results of the multivariate analysis. Hospital thromboembolism carries the highest risk ratio. The effect of size of the valve prosthesis has become nonsignificant, and hypertension is borderline significant. If included, preoperative endocarditis is also a significant independent variable for thromboembolism. The other factors remain highly significant. Although atrial fibrillation was the main reason to prescribe warfarin sodium, an interaction term between those 2 factors did not result in a significant effect ($P = .29$).

Discussion

Thromboembolism after aortic valve replacement was the most important valve-related postoperative complication. These events, however, could be associated with factors other than valve type.[2-5] Whatever the origin might be, thromboembolism after aortic valve replacement with a bioprosthesis was regarded as of more importance than structural failure.[6] The annual rate of thromboembolic events in studies using several valve types ranged from 0.9% to 2.2%,[2-6] which was comparable with those in our series.

Preoperative medically treated endocarditis in our patient population was considered a separate condition. High hospital mortality and annual rate of thromboembolism were found after valve replacement for endocarditis.[7,8] One possible explanation is damage of the endocardium during infection, creating procoagulant conditions. Regular ultrasonographic control after valve replacement is considered necessary in these patients.

Other valvular factors, such as a valve size of 27 mm or larger, had a significant effect on postoperative thromboembolism only in a univariate analysis. Larger valve size was not identified as a risk factor in a previous series.[2] Most series on valve size concerned the effect of the use of smaller valves and reported mainly on survival.[9,10] Neither the type and severity of aortic valve disease[2] nor rereplacement had significant effects on postoperative thromboembolism.[2]

None of the investigated coronary factors had a significant influence on postoperative thromboembolism. Previous CABG could not be identified as a risk factor after aortic valve replacement with a Medtronic Hall valve.[2] Nevertheless, crossclamping time and total bypass time[11,12] and a recent myocardial infarction[13] were previously identified as significant risk factors for postoperative stroke after CABG.

The role of atrial fibrillation in the occurrence of thromboembolism remains a matter for debate. No increase in thromboembolism was found in patients with a Medtronic Hall valve and preoperative or postoperative atrial fibrillation,[2] yet the long-term risk for thromboembolism was considerably higher in patients with atrial fibrillation undergoing CABG[13] or aortic valve replacement with a Hancock porcine bioprosthesis.[14] In our and other[14,15] patient groups, atrial fibrillation was the main reason for therapy with warfarin sodium. The effect of warfarin sodium in a series of patients after aortic valve replacement with a Carpentier-Edwards pericardial bioprosthesis was studied earlier: an annual rate of thromboembolism of 0.8% with salicylic acid, of 1.5% with no treatment, and of 2.9% with warfarin sodium was observed in retrospect.[16] This was considered as not significant, but a trend is clearly visible ($P = .07$) and was comparable with the current results. Treatment with salicylic acid is to be recommended for patients with a pericardial valve, and the presence of atrial fibrillation requires more frequent ultrasonographic control for detection of intra-atrial thrombus formation.

In a previous analysis[2] hypertension, smoking, and diabetes were identified as risk factors for ischemic cerebrovascular events, which were labeled as "arterial" and therefore unlikely to be altered by the intensity of anticoagulation. Moreover, use of peroral anticoagulants is considered as a serious condition with increased mortality.[17]

A history of preoperative CVA and the occurrence of hospital thromboembolism were also identified as significant independent factors after aortic valve replacement in octogenarians.[18,19] One could link these risk factors with carotid artery disease. A negative duplex scan result of the carotid artery, which is considered a reliable diagnostic tool,[20] does not exclude intracranial vasculopathy. Carotid lesions were not a significant factor for postoperative thromboembolism, although in another series asymptomatic patients with stenosis of the carotid artery of 80% had significantly more ischemic events.[21] Therefore symptomatic patients with carotid artery stenosis benefit from endarterectomy of the carotid artery. No study directly showed the consequences of lesions of the carotid artery for neurologic thromboembolic events after aortic valve replacement, however.

Hypertension, another vascular factor, was previously identified as the most important predictor for postoperative stroke[11,12,22,23] and must be controlled tightly. Age in our population was not a significant factor, probably because our population was considerably older compared with those of other studies.[2,24]

Current and previous results indicate clearly that the origins of thromboembolism after aortic valve replacement, with or without association of a CABG, are multiple. After valve replacement, regions of relative stasis and of flow with high velocity in varying degree were demonstrated in all prostheses.[25] A postulated mechanism for thromboembolism is platelet activation induced by shear stress, with adherence to the valve prosthesis and to the atheromatous plaques on vessel walls. Subsequent embolization to the cerebral blood flow could be responsible for thromboembolic events, even with small carotid lesions. It seems that the definition of thromboembolic events offered in the guidelines[1] remains partially valid. Atrial fibrillation and use of warfarin sodium, which targets the coagulation system,[2] do not play a role in this hypothetic sequence of events, which explains partly our counterintuitive results. A trend toward reduction of fatal thromboembolic events is observed with acetylsalicylic acid. Moreover, we could assume that small cerebral emboli go unnoticed. Warfarin sodium could facilitate hemorrhagic transformation, which could be held responsible for these neurologic events be-

TABLE 3. Simultaneous relationship between the prognostic factors and the risk of thromboembolism obtained with the Cox proportional hazards analysis

Factor	Risk ratio	95% CI	*P* value
Cerebrovascular accident	4.8	1.8-12.6	.0016
Warfarin sodium	3.0	1.5-6.3	.0028
Hospital thromboembolism	6.1	1.4-26.5	.016
Arterial hypertension	2.7	0.9-7.8	.063

CI, Confidence interval.

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coming symptomatic. This chain of events will probably remain hypothetical because it is not feasible to perform regular computed tomographic scans for every patient with a pericardial valve to detect all emboli. Nevertheless, implantation of aortic valve prostheses can be considered a minor contributor to cerebrovascular events.

We therefore recommend that use of acetylsalicylic acid should be promoted strongly, especially in patients with larger valve size or previously treated endocarditis. The long-term use of warfarin sodium after aortic valve replacement with a bioprosthesis could be cautiously considered in elderly patients with atrial fibrillation and previous thromboembolic events. These patients should receive regular ultrasonographic control. Hypertension should be controlled tightly. If a tissue valve for a certain patient is indicated, a Carpentier-Edwards pericardial valve can be recommended.

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